

Implementing Comprehensive PMTCT and HIV Prevention for South African Couples

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PROTOCOL TEAM ROSTER

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STUDY MANAGEMENT

All questions concerning this protocol should be sent to djones@med.miami.edu via e-mail. A response should generally be received within 24 hours (Monday-Friday).

Clinical Management

This study will not be managing provision of medication to participants.

Laboratory

Physical health data will be obtained from clinic records to assess disease status (i.e., CD4 cell count) and provide patients with appropriate feedback. Dried blood spots (DBS) will be used to assess adherence to ART lifelong medications (Tenofovir, Lamivudine, Emtracitabine, Stavudine, Lopinavir, Ritonavir, Efavirenz) for mothers at 32 weeks gestation or short term PMTCT ARVs (Nevirapine, Zidovudine) for 6 week old infants. The HSRC will oversee provision of laboratory services and oversee data management and provision of data to the US site.

Data Management

For nonclinical questions about inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the SA Principal Investigator, Karl Peltzer. Send an e-mail message to KPelzer@hsrc.ac.za Attention: Karl Peltzer. Include the protocol name and a detailed question.

Randomization

This study will randomize community health centers, stratified by antenatal clinic care volume, using a computer randomized program of random numbers.

Computer and Screen Problems

For questions regarding data entry/collection contact Ryan Cook, US Data Manager at (305) 243-2188. Queries on questionnaire items should be addressed to the US Principal Investigator Deborah Jones via e-mail djones@med.miami.edu or phone (305) 243-2041.

Protocol Document Questions

For questions concerning the protocol document, contact the US Principal Investigator. Send an e-mail message to djones@med.miami.edu ATTN: Deborah Jones.

Copies of the Protocol

To request a copy of the protocol, send a message to Deborah Jones via e-mail djones@med.miami.edu.

Adverse Event (AE) Questions

For questions regarding reporting of adverse events, contact the US Principal Investigator Deborah Jones, via e-mail djones@med.miami.edu

Product Package Inserts or Investigator Brochures

This study will not provide products, package inserts or brochures.

Study Drug

This study will not provide study drugs or medications to participants.

IND Number or Questions

This study will not require an IND or utilize investigational drugs.

Study Drug Orders

This study will not utilize study drugs.

Phone Calls

For questions regarding the documentation of phone calls, send a message to the SA Principal Investigator, Karl Peltzer, kpeltzer@hsrc.as.za.

Protocol-Specific Web Page

This study will not utilize a web page

ACRONYMS

ACASI	Audio computer assisted self interview
ART	Antiretroviral therapy
ARV	Antiretroviral
CRF	Case Report Form
DHHS	Dept. of Health and Human Services
HCT	HIV Counseling and Testing
HIV	Human Immunodeficiency Virus
IPV	Intimate Partner Violence
IRB	Institutional Review Board
MI	Male Involvement
OI	Opportunistic Infection
PI	Principal Investigator
PID	Personal Identification
PMTCT	Prevention of Mother to Child Transmission
PSMR	Participant Status Monitoring Report
REC	Research Ethics Committee
SID	Site Identification
SOC	Standard of Care
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
T	Timepoint

Implementing Comprehensive PMTCT and HIV Prevention for South African Couples SAPMTCT

1.0 INTRODUCTION

This full factorial, controlled study design will test the effectiveness of the piloted behavioral intervention to significantly increase PMTCT uptake among rural HIV positive pregnant women, simultaneously determining whether the intervention conducted both with or without the participation of male partners will have an additive or synergistic impact on PMTCT uptake. The intervention will utilize a combination of both group and individual or couples counseling strategies, ante – and postnatally, with a 12 month followup assessment of infant serostatus. During antenatal care, the intervention will use a group format to address key issues related to enhancing PMTCT uptake, including PMTCT information, HIV disclosure, coping with stigma, intimate partner violence, adherence to the overall PMTCT protocol and safer conception practices. Just prior to birth and postpartum, the intervention will shift to an individual or couples-based counseling format, targeting medication adherence, safer infant feeding, family planning and safer conception practices (Desclaux & Alfieri, 2009; Makanani et al., 2009). As one of the key goals of the PMTCT protocol, the intervention will facilitate the uptake of safer conception practices by integrating and enhancing the role of health care providers in the delivery of family planning services for women or couples living with HIV.

1.1 Primary Aims

Aim 1: to increase uptake and adherence to ante-, peri- and post-natal PMTCT protocols by HIV positive pregnant women through the implementation of a comprehensive, evidence-based risk reduction, medication adherence and PMTCT intervention.

Aim 2: to retain women and infants in post-natal care to ensure adherence to PMTCT safe infant feeding protocols (SA DOH, 2010).

Aim 3: to improve sexual and reproductive decision making and safer conception practices.

Aim 4: to assess the impact of male engagement on PMTCT uptake (medication adherence, feeding practices, clinic attendance), safer sex and family planning practices.

1.2 Significance

Prevention of Mother to Child Transmission (PMTCT) strategies have dramatically reduced infant morbidity and mortality associated with HIV, as well as significantly improved maternal health (Theuring et al., 2009). Computer modeling estimates indicate that 90-95% participation in PMTCT plus effective pharmacologic regimens (Torpey et al., 2012) would reduce infant HIV incidence to the WHO (2008) goal of < 5% (Ciaranello et al., 2012). Guidelines for antiretroviral (ARV) prophylaxis and combination ARV therapies (cART) to reduce MTCT have been implemented in most HIV-affected countries (UNAIDS, 2012). Despite PMTCT availability, however, not all pregnant women are tested (Van Lettow et al., 2011; Stringer et al., 2008; Larrson et al., 2012; Peltzer et al., 2010b; 2009), not all women receive treatment (Goga et al., 2012), not all mothers provided with medication take it themselves or provide it to their newborns (WHO, 2012; Laher et al., 2012) and not all newborns are tested (SA DOH,

2010; WHO 2012). A meta-analysis of PMTCT studies in 15 sub-Saharan countries also identified differences in PMTCT uptake by pregnant women by method, e.g., HIV opt-out testing uptake in antenatal care exceeded opt-in (94% vs. 58%); for those eligible, ARV prophylaxis coverage exceeded cART treatment (70% vs. 62%); among infants exposed to HIV, early HIV testing exceeded repeated testing at age 12 and 18 months (64% vs. 55%; Wettstein et al., 2012). In addition, pooled analysis of PMTCT adherence studies indicated only an estimated 74% of pregnant women had adequate (>80%) ART adherence: Antenatal exceeded postpartum adherence (76% vs. 53%; Nachega et al., 2012).

In South Africa, although progress has been recorded in the implementation of PMTCT programs, these improvements have, for the most part, occurred in urbanized areas, with rural areas remaining at unacceptably high levels of MTCT (see also Wettstein et al., 2012). Lack of paternal support, stigma, lack of testing or disclosure, gender dynamics, Intimate Partner Violence (IPV), little PMTCT information, clinic access and poor retention in care have been identified as major challenges to PMTCT effectiveness in rural areas (e.g., Tabana et al., 2012; Mephram et al., 2011; Bancheno et al., 2010; Bajunirwe et al., 2005; Jones et al., 2005; Rollins et al., 2007; Rutenberg et al., 2003). South Africa's Mpumalanga Province, the proposed site for this application, is predominantly rural and has one of the highest antenatal clinic (ANC) HIV prevalence rates (37%) in the country. Mpumalanga's Gert Sibande District reported the highest ANC HIV rate nationwide, 46%, an increase of 7.9% since 2009 (NDOH, 2012). Mpumalanga has one of the lowest rates of PMTCT participation; fewer pregnant women participate in PMTCT services and many (23%) report mixed feeding (Ukpe et al. 2009). While recent reports on South Africa's PMTCT Programme to reduce transmission to the WHO 2010 goal of < 5% have been promising (Goga et al., 2012), these 2010 PMTCT effectiveness estimates were primarily drawn from urban clinics and did not include "very sick infants" or children who were not immunized at 6 weeks. In contrast, Mpumalanga Province infant HIV PCR data at 6 weeks from all clinics in the final quarter of 2011 indicated wide variations in clinic rates of HIV infected infants (5 - 47%, median 13%), higher rates than in 2010, and higher rates of HIV infected infants in follow up testing up to one year (an additional 6 - 22%; National Health Laboratory, 2011). Retention in care remains low (Horwood et al., 2010), infant care may be delayed (Cooke et al., 2009) and recent reports suggest breastfeeding may be responsible for more than half of new pediatric HIV infections (Van de Perre et al., 2012), highlighting the need for behavioral change interventions (NDOH, 2012) to promote safer infant feeding practices (Goga et al., 2011) in combination with ARV adherence (Hudgens et al., 2012). This application is designed to test the efficacy of a piloted intervention strategy to significantly increase uptake of PMTCT by rural HIV positive pregnant women (Peltzer et al., 2011), evaluating the relative contribution of male partners in achieving the goals of PMTCT (<5%) in high MTCT ($\geq 13\%$) clinics.

Ante-, peri- and postnatal care & safer feeding. Two thirds of newborn deaths could be avoided by utilization of existing maternal, newborn and child health policy packages, e.g., family planning, PMTCT, skilled birth attendance or clean childbirth, early identification of illness, safer infant feeding, and PMTCT through ARVs (WHO & Partnership for Maternal, Newborn and Child Health; PMNCH, 2006). Yet, mothers may delay ARV onset (Chibwesha et al., 2011) and mothers and newborns often miss postpartum visits and spend most of the postnatal period (0-6 weeks) at home, increasing the risk of maternal or neonatal mortality (Landes et al., 2012; Walker et al., 2012). Attendance at antenatal care may be limited to only one visit (Myer et al., 2012), and poor retention in postpartum care is common (Dube et al., 2012; Kim et al., 2012; Watson-Jones et al., 2012; Chetty et al., 2012). WHO recommends a minimum of four antenatal and four postnatal visits for all HIV positive pregnant women (PMNCH, 2006), e.g., targeting immunizations, interventions, treatment. Mothers may also need additional guidance on infant feeding (Maman et al., 2012) as a single session appears insufficient to sustain the benefits of safer infant feeding (Bequet et al., 2012; Little et al., 2012; Natchu et al., 2012;

Ochola et al., 2012). In low and middle-income countries, only 39% of pregnant women received => 4 antenatal visits during 2000–2008, and in Africa, less than half of the poorest 20% of women have access to any antenatal care (WHO, 2012). Adherence to PMTCT protocol at 6 weeks postnatal is low (e.g., Uganda, 38%), and previous adherence to routine care, perception of benefit, access and the presence of spousal support appear to be important motivators for postnatal adherence (Nassali et al., 2009).

PMTCT program failure and dropout occurs at all stages of the ante-, peri- and postnatal process in South Africa (DOH, 2010; Rispel et al., 2009; Clouse et al., 2013; Sengayi et al., 2013). Implementation of PMTCT programs in overburdened clinics presents multiple challenges, including individual [e.g., denial, depression, maternal failure to ingest medication or provide it to the infant, failure to obtain antenatal or infant testing (e.g., Goga et al., 2012)], interpersonal [e.g., lack of male involvement, IPV (Ghanotakis et al., 2012), alcohol or drug use (Tumwesigye et al., 2012)], social [e.g., stigma, (Mephram et al., 2011), lack of disclosure (Kuonza et al., 2011; Turan et al., 2011; 2012; Hardon et al., 2012)], and systemic factors [e.g., home delivery, delayed access to care (Laher et al., 2012)].

PMTCT uptake and male “involvement.” Integration of PMTCT with existing services and increasing male participation in antenatal care have been proposed to enhance PMTCT uptake (e.g., Peltzer et al., 2010a, b, c; Conkling et al., 2010). While men are the traditional sexual and reproductive decision makers, the impact of male involvement in PMTCT remains unclear and untested (Montgomery et al., 2011; Brusamento et al., 2012). Taking full advantage of male support may also require a level of communication and cooperation among couples that enables mutual disclosure of HIV status (Dageid et al., 2012). Given the high potential for conflict and IPV, uptake may be limited by lack of HIV status disclosure (Villar-Loubet et al., 2012a; Peltzer et al., 2010d). However, while previous studies were unclear as to what constitutes effective male “involvement”(MI), its measurement and its objectives (Montgomery et al., 2012), effective MI is here operationalized as clinic attendance, spousal support, communication, HIV/PMTCT knowledge and HIV testing and disclosure with the objective of facilitating uptake of PMTCT pre- and postnatal practices.

Studies to evaluate the impact of male involvement have been limited (Sherr & Croom et al., 2012), used varied methods (Byamugisha et al., 2010), and had mixed results. Media campaigns used to increase MI from 4% to 11% (Botswana); couples HIV Counseling and Testing (HCT) has been used to increase MI (Zambia; Wall et al., 2012). MI has increased ANC attendance and HCT (Mohlala et al., 2011), decreased unprotected sex during pregnancy and increased ANC attendance by 9% (South Africa; Mohlala et al., 2011). Increased MI has been associated with nevirapine uptake (Tanzania; Becker et al., 2009), decreased MTCT (Kenya; Alusio et al., 2011) and increased clinic attendance by 15% (Zambia; Katz et al., 2009 a,b). Couples counseling in pre- and postnatal care has facilitated communication about HIV serostatus (Cote d’Ivoire; Desgre’es-Du-Lou et al., 2009), addressed barriers to ARV uptake for mothers and their newborns (Kenya: Farquhar et al., 2004; Alusio et al., 2010), encouraged adoption of safer conception strategies among sero-discordant couples (Orne-Glieman et al., 2010), and reduced vertical transmission (Kenya; Alusio et al., 2011). In Rwanda and Zambia, couples counseling enhanced follow up but not Nevirapine uptake (Conkling et al., 2010). Women have responded positively to male involvement (Cameroon; Nkuoh et al., 2013). Despite these results, no trial has definitively tested the effect of MI on PMTCT uptake (Montgomery et al., 2012).

While attendance by couples is feasible (Becker et al., 2009), ANC attendance by men may be “necessary but not sufficient” to influence PMTCT. A review of studies in Africa involving men in antenatal care concluded that male “support” as well as “involvement” may determine increased PMTCT uptake (Auvinen et al., 2010). Men possess general HIV knowledge but lack specific information regarding PMTCT (South Africa; Villar-Loubet et al., 2012) and feel unable to attend antenatal clinics due to work schedules (Tanzania; Falnes et al., 2011). Men also may regard ANC

health facilities as being “generally unfriendly” to them (Botswana; Letshwenyo-Maruatona, 2012). Men are perceived as decision makers in the home, and feel their position is undermined if they are expected to attend a “women’s clinic program,” leading them to decline to attend ANC visits with their partners (Orne-Glieman et al., 2010; Theuring et al., 2009; African Development Bank, 2009), with as few as 2% attending ANC (personal communication, Provincial Health Office, Lusaka, Zambia, 2012).

Disclosure, Stigma and Intimate Partner Violence (IPV). Following diagnosis of HIV infection, partners may not disclose their HIV serostatus (Simbayi et al., 2007; Vu et al., 2012). Women may fear rejection, abandonment, violence, stigmatization, loss of respect or scapegoating within intimate relationships if serostatus questions are raised (Abrahams & Jewkes, 2012; Sethosa et al., 2005; Bouillon et al., 2007; Deribe et al., 2008; Peltzer, 2011; Rujumba et al., 2012). Men have similar concerns regarding rejection and blaming (Villar-Loubet et al., 2012) as well as exposure of their own sexual behavior (Deribe et al., 2010). The threat of intimate partner violence (Peltzer et al., 2010d; Hyginus et al., 2012; Russell et al., 2012; Shamu et al., 2011; Villar-Loubet et al., 2012; Moses et al., 2012) associated with disclosure during pregnancy may therefore impede access to care during pregnancy and PMTCT uptake (Visser et al., 2008). The initial disclosure of positive test results is one of the greatest stressors experienced following an HIV diagnosis (Jones, 1998). Those who anticipate that others will respond supportively may approach both testing and diagnosis with less anxiety and more constructive planning. Those expecting strong negative reactions from others may respond less adaptively (e.g., by social withdrawal) or may avoid receiving test results (SA DOH, 2010). However, both men and women assert that they do not want to be “pushed” to disclose (Villar-Loubet et al., 2012).

In sub-Saharan Africa, IPV has been associated with HIV infection (Ackerman et al., 2002); significant overlap exists between women who are seropositive and those who are battered (Shamu et al., 2011). The prevalence of IPV among pregnant women in South Africa is one of the highest reported globally; risk factors include HIV infection, history of violence, alcohol, and drug use (Shamu et al., 2011; 2012). The ability to disclose HIV serostatus and negotiate safer conception practices is key to controlling transmission, but women are restricted by traditional gender role constraints (Melendez et al., 2003), e.g., antenatally, women with violent or controlling male partners are at increased risk of HIV infection, and more likely to have risky sexual practices imposed upon them during pregnancy (Dunkle et al., 2004). The occurrence of IPV during pregnancy (Makayoto et al., 2012) and gender based power dynamics within couples (Groves et al., 2012; Langen, 2005) have become a serious impediment to accessing PMTCT and to women’s health overall. Our pilot study (Peltzer et al., 2012) identified high rates of IPV among pregnant couples; following intervention, all forms of IPV by men decreased. This application proposes a gender-based group intervention plus couples counseling to directly address IPV, disclosure and stigma, key elements to facilitating PMTCT uptake.

Safer Conception Practices (SCP), Contraception and Family Planning. One of the major components of the PMTCT “cascade” is provision of reproductive health choices to enable either the prevention of unintended pregnancies or appropriate planning for intended future pregnancies for women living with HIV (Expert Committee, 2011, DOH, 2010). Many women in sub-Saharan Africa spend the majority of their adult lives pregnant (Mugo et al., 2011) and the majority of women living with HIV are diagnosed during their reproductive years (15- 45 years). As seropositive women initiate or continue childbearing (Westreich et al., 2012; Schwartz et al., 2012; Jones et al., 2010; Harrington et al., 2012), “safer” conception practices [e.g., the use of ART to reduce infectiousness (Cohen et al., 2011), pre-exposure prophylaxis (PreP) to reduce acquisition (Vernazza et al., 2011; Matthews et al., 2012), timed unprotected intercourse (Matthews et al., 2009; Mmeje et al., 2012)], and use of dual contraception (Peltzer et al., 2010; Seutlwadi et al., 2012) are essential to reduce the elevated risk of

transmission during conception, pregnancy (Mugo et al., 2011) and postpartum. Complex reproductive strategies and high rates of unplanned pregnancy (Wanyenze et al., 2013; Holt et al., 2012; Goga et al., 2012; Peltzer, & Shikwane, 2011) and sexual risk behavior (Peltzer & Mlambo, 2013) underscore the need to facilitate the integration of PMTCT, safer conception, dual contraception and family planning during ante- and postnatal care (SA DOH, 2010; Lindegren et al., 2012; Schwartz et al., 2012; Lazarus et al., 2013).

Factors limiting the use of safer conception practices are similar to those preventing PMTCT uptake, e.g., fear of HIV disclosure, stigma, and IPV (Taulo et al., 2009), including fears of judgmental healthcare providers with negative attitudes towards childbearing by HIV seropositive women (Barreri et al., 2007; Peltzer et al., 2009). When women do discuss fertility plans with providers, the extent to which safer conception methods are included is unclear (Sofolahan et al., 2013). In Cape Town, while over 30% of HIV positive women wanted additional children, and 60% in Johannesburg planned to conceive in the next year, in both regions, most had never had a conversation with a health care worker on this issue (Schwartz et al., 2012). The proposed intervention utilizes guidelines on safer conception (Bekker et al., 2011) and contraception (Lopez et al., 2010) delivered through combined group, individual and/or couples-counseling interventions to address family planning and the uptake of safer conception practices in conjunction with pre- and postnatal clinical care.

This application addresses limitations in rural PMTCT uptake and proposes a controlled study to evaluate the effectiveness of an intervention to reduce mother to child transmission using prenatal groups and pre- and postnatal individual and couples counseling as well as to assess the impact of male involvement on PMTCT uptake during pre- and postnatal care. Study objectives are a) to maximize PMTCT protocol adherence and retention in care antenatally to 12 months postnatally, and b) to introduce contraception, family planning and safer conception practices into the pre- and postnatal PMTCT protocol. The program extends the existing public health program linking antenatal HIV Counseling and Testing (HCT), PMTCT and family planning services, focusing on reducing barriers to PMTCT that have resulted in unacceptably high levels of MTCT.

1.3 Impact & Innovation

Despite the availability of an effective PMTCT treatment protocol and infant feeding guidelines designed for PMTCT, uptake in rural South Africa remains suboptimal (SA DOH, 2011). We hypothesize that PMTCT uptake will be significantly improved by a comprehensive intervention combined with the active engagement and support of male partners in the PMTCT process. Our pilot study was designed to increase male partner involvement in PMTCT to reduce perceived barriers to adherence to the ante-, peri- and postnatal PMTCT protocols. Results confirmed that men will actively participate in an intervention that supports their female partner's participation in PMTCT and promotes the reduction of sexual risk behaviors and IPV (see Preliminary Studies: Villar-Loubet et al. 2012). While the small sample size of HIV seropositive women in the pilot study precluded definitive conclusions, it provided important guidance and direction for the design of the proposed study and for the refinement of our intervention strategy to target medication adherence, partner communication, mutual HIV status disclosure, reduction of IPV, family planning, safer conception and safer infant feeding practices.

This grant program seeks to enhance PMTCT uptake pre- and postpartum and reduce MTCT in Community Health Centers in rural Mpumalanga Province, with the goal of significantly reducing current vertical transmission rates of $\geq 13\%$ to $< 5\%$ among infants at 6 weeks and 12 months of age. Using a sustainable strategy (Peltzer et al., 2010; 2012; Ndou et al., 2012; Uwimana et al., 2012) of training

existing CHC staff e.g., antenatal nurses & HCT counselors, to provide counseling in both group and individual sessions tied to regular antenatal and postnatal clinic visits, the application integrates sexual health, family planning and contraception, the prevention of unintended pregnancies as well as planning for intended future pregnancies, one of the goals of the PMTCT “cascade” (Expert Committee, 2011, SA DOH, 2010; Harrington et al., 2012; Goga et al., 2012; Suthar et al., 2013).

Implementation of the intervention by CHC personnel provides the foundation for rapid translation and scale-up of the program. If successful, the “Protect Your Family” intervention will provide a generalizable integrated, sustainable model for clinics with high rates of HIV and high incidence of MTCT to optimize PMTCT program delivery and effectiveness, which would have major health policy implications for containing the epidemic in two of the most vulnerable affected populations in rural South Africa: HIV seropositive pregnant women and their infants.

Innovation: While there have been studies attempting to illustrate the contribution of male participation to PMTCT uptake, as well as behavioral interventions to promote the PMTCT process, this application proposes to capitalize on the findings of our recent efficacy pilot study to determine the relative effectiveness of both strategies, individually or collectively, in promoting PMTCT uptake in rural South Africa. This full factorial, controlled study design will test the effectiveness of the piloted behavioral intervention to significantly increase PMTCT uptake among rural HIV positive pregnant women, simultaneously determining whether the intervention conducted both with or without the participation of male partners will have an additive or synergistic impact on PMTCT uptake. The intervention will utilize a combination of both group and individual or couples counseling strategies, ante – and postnatally, with a 12 month followup assessment of infant serostatus. During antenatal care, the intervention will use a group format to address key issues related to enhancing PMTCT uptake, including PMTCT information, HIV disclosure, coping with stigma, intimate partner violence, adherence to the overall PMTCT protocol and safer conception practices. Just prior to birth and postpartum, the intervention will shift to a individual or couples-based counseling format, targeting medication adherence, safer infant feeding, family planning and safer conception practices (Desclaux & Alfieri, 2009; Makanani et al., 2009). As one of the key goals of the PMTCT protocol, the intervention will facilitate the uptake of safer conception practices by integrating and enhancing the role of health care providers in the delivery of family planning services for women or couples living with HIV.

1.3.1 Theoretical Framework and Theoretical Training Model

Model. The intervention applies the Information Motivation Behavioral Skills (IMB) model to the objectives of the PMTCT protocol (PMTCT related-information, motivation to engage in PMTCT, and behavioral skills to prevent transmission), to promote PMTCT uptake (Fisher et al., 2006). The intervention provides Information on PMTCT (realistic expectations for medication, side effects, treatment duration, the relationship between PMTCT, ARVs, viral load, CD4, infant feeding and HIV transmission) that enhances treatment Motivation (positive attitudes on medication and engagement in care and treatment) and Behavior (increased health care attendance behaviors, coping with stigma and disclosure) to increase adherence to treatment and retention in care. This process promotes positive health outcomes and provides Information (e.g. prevention of MTCT, viral load suppression, subjective perceptions of improved health, reduced distress) that increase Motivation to maintain adherence Behavior to the PMTCT protocol over time (Fisher et al., 2008). The IMB model has been applied in a variety of HIV+ and chronic condition patient populations and settings (e.g., Amico, 2011; Starace et al., 2006; Amico, 2006; Fisher et al., 2006), including those with limited health literacy (Fisher et al., 2008).

1.3.2 Preliminary Studies

This application is based on the extensive HIV research experience of our team (Drs. Jones, Peltzer, Weiss) in the US and international settings on medication adherence, PMTCT, and sexual risk reduction among HIV negative and seropositive men and women and serodiscordant couples. Drs. Jones and Peltzer led the PEPFAR PMTCT pilot study in South Africa; Dr. Peltzer is an expert on PMTCT in South Africa; Drs. Weiss and Jones are co-creators of the behavioral risk reduction intervention proposed in this application.

Promoting Male Involvement to Improve PMTCT Uptake, PI D Jones, CoPIs K Peltzer, S Weiss (NIH/PEPFAR P30AI073961-S). This one year pilot project (n = 239 couples) provides the foundation for this application. Although the number of women with HIV (n = 76) was too small to derive meaningful statistical comparisons on most findings, the clinical outcomes were sufficiently compelling to provide guidance and direction to the development of this application. Pregnant women and their partners from antenatal clinics in Mpumalanga Province, South Africa were followed from month 4 of pregnancy to 3 months postpartum. Project aims were to increase male involvement in ANC to promote PMTCT and to reduce unprotected sex during pregnancy. Men participated in both experimental and control conditions. The experimental condition included a gender-concordant group intervention based on sexual risk reduction and PMTCT promotion, and the attention-control condition included time-matched usual antenatal care. Baseline findings identified multiple sex partners, high levels of unprotected sex (50%) and IPV among both men and women, and low levels of knowledge about HIV transmission and PMTCT among men (Peltzer et al., 2011). Post-intervention, men had high rates of ANC attendance in both conditions (Experimental: 86%; Control: 79%). Experimental participants decreased unprotected sex at follow up in comparison with control participants ($F = 7.16, p = .008$). Adjusting for baseline levels, rates of unprotected sex at post-intervention were 32% and 83%, respectively, in experimental and control conditions; mixed estimates of unprotected sex using regression pretest-posttest, adjusting for baseline values, indicated an intervention effect estimate of -0.511, i.e., a 51% reduction in rates of unprotected sex, intervention versus control, assuming an adjusted intra-class correlation (ICC) of 0.14 (Jones et al., 2013). Qualitative data from both genders reflected concerns about serostatus disclosure and communication (Villar-Loubet et al., 2012a). There was an increasing trend in positive communication and a decrease in the number of sex partners (Villar-Loubet et al., 2012b). Four infants were HIV+ by PCR at 6 weeks (1 experimental, 3 control). In the experimental group, HIV-related knowledge increased ($F(1, 451) = 23.52, p < .001$) and intimate partner violence by men and negative communication by women decreased ($F = 6.94, p = .009$; $F = 9.30, p = .003$; Jones et al., 2013). Mixed infant feeding, not an intervention target in this pilot study, was practiced by 40% of women. The current application will promote safer feeding practices, i.e., exclusive breast feeding or replacement feeding, and continue to target attendance, sexual risk reduction and safer conception.

Programme to Improve Implementation of the Prevention of Mother to Child Transmission of HIV in Cacadu District of the Eastern Cape and in Gert Sibande and Nkangala Districts of Mpumalanga Province, South Africa. PI, K Peltzer (Overall PI L Simbayi) (CDC-PEPFAR: USG PS000570). This project aimed to improve PMTCT adherence by evaluation of PMTCT program activities. Identified gaps in PMTCT delivery: Low clinic uptake of Nevirapine (56%). Missed opportunities: HCT among 67% women during pregnancy. Shortcomings identified included health policy, service delivery & health-seeking behavior (Peltzer et al., 2010); other factors identified included high levels of traditional and complementary health practices (Peltzer et al., 2009), IPV and HIV risk (Rispel et al., 2009), barriers to HIV testing (Peltzer et al., 2010b), problems with infant feeding and testing (Ladzani et al., 2011; Peltzer & Mlambo, 2010a) and adherence to ARV prophylaxis (Peltzer et

al., 2010c; Peltzer et al., 2011), lack of family planning services (Peltzer et al., 2009), and problems with HCT provision (Peltzer et al., 2011). An intervention was used to strengthen PMTCT services and awareness. Long clinic waits and short counseling sessions remained (Rispel et al., 2009).

Improve Capacity of an Indigenous Institute to Enhance Monitoring & Eval. of HIV/AIDS in SA, PI, K Peltzer (CDC-PEPFAR: USG PS000570). This project sought to stimulate male participation in PMTCT in Mpumalanga using community campaigns with male peer mentors in 3 sub-districts. Community mobilization, i.e, door to door campaigns, CHC health talks, were conducted over 6 months; 3300 men were recruited. Only 6% of men attended ANC with partners, 2% also attended HCT with partners. Couples (n = 170) participated in a 3 session program (Peltzer et al., 2011). Barriers included lack of weekend clinic access for working men, disconnect from the “maternal” program, concern about HCT, partner disclosure and gender specific services.

Research and intervention for prevention-of-mother-to child transmission in a resource poor setting. PI, K Peltzer (Ford Foundation). This study identified barriers to care and provided health systems support interventions. Factors influencing PMTCT adherence and outcomes were identified (Peltzer et al., 2006, 2007, 2009, 2010c). Intervention studies found positive impact of PMTCT interventions, e.g, training of traditional birth attendants (Peltzer, 2006), maternal self-medication with nevirapine tablets at onset of labor, and maternal provision of nevirapine syrup to newborns (Peltzer et al., 2008).

Efficacy of a lay health worker led group antiretroviral medication adherence training among non-adherent HIV-positive patients in KwaZulu-Natal, South Africa. PI K Peltzer, CoPIs, D Jones S Weiss (TIBOTEC REACH Initiative). The effectiveness of lay health worker-led groups to improve ART adherence in adults was assessed in a randomized controlled trial at a district hospital HIV clinic in Mpumalanga. Low adhering patients on ART (n = 152) attended three group sessions plus standard of care, or standard of care alone. Adherence knowledge pre- to post increased in the intervention condition compared to standard of care. Adherence and CD4 count increased and depression decreased in both conditions (Peltzer et al., 2012).

Interventions to Enhance HIV Medication Adherence in Zambia. D Jones, PI, I Zulu, S Weiss, N Chitalu, Co PIs (R21AI067115). This clinical trial sought to increase adherence among naïve ARV users in Zambia (n=140) utilizing a 3 session psychoeducational group; most participants reported 100% adherence; 15% reported non-adherence over 3 months. Pharmacy records, pill count, patient report and provider evaluation were triangulated to evaluate adherence. The number of sessions attended, drop out rate and health care appointments attended did not differ between conditions, while participants in the intervention condition reduced the number of missed doses and maintained the reductions over time ($F = 2.37$, $p = .04$) in comparison with the individual condition (Jones et al., 2012).

Barrier Acceptability among Culturally Diverse HIV+/- Women and their Partners (The NOW/NOW2 Projects), PI S. Weiss, CoPIs N Chitalu, D Jones (NIMH RO1MH63630). This study enrolled 1080 HIV + and HIV- high risk women in Miami, USA and Lusaka, Zambia and sought to reduce risk of HIV/STD transmission, infection, and re-infection among HIV+/- women (Jones et al., 2001, 2004, 2007). The four weekly session intervention increased barrier acceptability and acceptability predicted use in both US ($F(8,40) 3.79$, $p = .002$) and Zambia ($F(8,66) 3.21$, $p = .004$). Participants increased use and acceptability of female condoms and maintained condom use at 6 and 12 months. Intervention participants increased male condom use at 6 months (reduced to non-significant “trend” at 12 months) and reduced sexual risk behavior (Jones et al., 2006).

Implementing HIV Risk Reduction in Zambia (Partner/Partner 2 Projects), PI D Jones, Co-PIs S Weiss and N Chitalu, (NICHD/NIH R24HD43613; R01HD058481). This clinical trial (n= 420 Zambian couples) of a 4 week couples’ sexual behavior intervention found intervention women had higher condom use ($F = 5.68$, $p = .02$), more positive condom attitudes, increased plans for safer sex, and less alcohol use (Jones et al., 2005); female and male condom use increased at 6 months and was

maintained over 12 months (Jones et al., 2008a). Communication and condom use increased among inconsistent users and was maintained over 12 months. HIV- men increased barrier use ($F = 16.13$, $p = .001$; Jones et al., 2008b). The study was translated to 6 Lusaka CHCs ($n = 420$ seropositive & seroconcordant couples); at 12 months follow-up couples had higher sexual barrier use ($F = 7.17$, $p = .001$; Jones et al., 2009; 2010; Vamos et al., 2012), couples sustained comparable positive results. The intervention is being disseminated nationwide in Zambia (Weiss et al., 2011).

2.0 STUDY DESIGN

Summary of Approach. This study is a group-randomized controlled trial using a 2 x 2 x 5 comparison Phase (Women-only, Couples) x Condition (Experimental, Control) x Time (Baseline, 32 weeks pregnant, 6 weeks and 6 and 12 months postpartum). Community health centers ($n = 12$ CHCs) in communities with high rates of vertical transmission ($\geq 13\%$) within the Gert Sibande and Nkangala Districts in Mpumalanga Province, South Africa, will be stratified by size and randomly assigned to condition in a 6:6 ratio. Study participants ($n = 2160$) will be 720 women in Phase 1 and 720 couples ($n = 1440$) in Phase 2. [N.B. Treatment protocols are in accordance with South African Clinical Guidelines for PMTCT.]

2.1 Formative Development: Adaptation of “Protect Your Family”

2.1.1 Adaptation of “Protect Your Family”. The PMTCT and safer conception components of the intervention were developed during our pilot study and earlier studies in Zambia (e.g., Jones et al., 2004), incorporating cultural factors that influence knowledge, attitudes and perceptions about conception and PMTCT. Core issues identified (Villar-Loubet et al., 2012a, 2012b; Peltzer et al., 2012) were integrated into the intervention sessions and reviewed by Dr. Peltzer and his team for cultural congruence. During the initial 3 months of the award, “Protect Your Family” will be collaboratively adapted by US and SA teams for the women-only arm (Phase 1) and the content of the couples sessions will be reviewed and refined, guided by experiences from the pilot study (e.g., Jones et al., 2013; Villar-Loubet et al., 2012a, 2012b;) as well as input from Drs. Peltzer and Dwane on SA cultural issues and from Drs. Jones and Weiss on strategies from earlier “women-only” and couples studies in Zambia (e.g., Jones et al., 2008c, 2010).

2.2 Site Selection Criteria, Training, and Involvement

2.2.1 Gert Sibande District/ Nkangala District. Study sites will be selected from Gert Sibande District (pop. 890,699, 71 PMTCT sites) and Nkangala District (pop. 1,020,592, 80 PMTCT sites) in Mpumalanga Province, the province with the highest rates of antenatal HIV prevalence in South Africa, i.e., 35.6% in 2009, 35.1% in 2010 (SA DOH, 2010, 2011). The clinics proposed from Gert Sibande and Nkangala Districts were selected in consultation with the Mpumalanga Provincial Department of Health (see Letters of Support).

Gert Sibande and Nkangala districts have had the highest antenatal HIV prevalence (35.6%, 30.1%) and lowest rates of HIV testing for infants (20.7%, 43.1%) in Mpumalanga [Health Systems Trust, (HST) 2009]. Only 70% of those mothers identified as seropositive took Nevirapine for PMTCT (SA DOH, 2010). Low rates of HIV testing during pregnancy (74.6%, 86.3%) were also found in 2009. While recent reports noted decreasing rates of mother-to-child

transmission in South Africa, these decreases are predominantly occurring in urban areas rather than rural locales, e.g., Mpumalanga.

2.2.2 Size matching and randomization. Clinic sites will be matched on antenatal clinic care volume and then randomized. All sites will meet South African criteria for PMTCT sites:

- on-site daily HCT
- ARV distribution & CD4 testing
- antenatal counseling on infant feeding
- postnatal counseling and infant feeding support, infant formula
- HIV infant testing
- \geq two trained PMTCT staff and 2 counselors
- support group for HIV-positive mothers and pregnant women

The MTCT rate mean = 17%, median = 13% for all 27 clinics. Sites selected will be from clinics in the upper 50%, i.e., \geq 13% MTCT rates, with sufficient numbers of HIV seropositive women receiving antenatal care to achieve recruitment goals.

2.2.3 Site Preparation. Ethical approval will be obtained prior to study onset from the Provincial Health Office. Drs. Dwane and Sifunda will review the objectives of the study with CHC staff, and discuss implementation strategies within the existing CHC framework. Senior CHC staff will identify staff candidates to be trained to conduct the intervention at their sites.

2.2.4 Site staff Recruitment, Assessment and Behavioral Intervention Training. Study personnel (counselors and assessors) will undergo formal training on recruitment, assessment, use of audio computer assisted self-interview (ACASI) technology and intervention procedures by the UM investigators (Jones, Weiss), HSRC intervention trainers (Sifunda, Mlambo, Matseke) and assessment trainer (Mohlabane). Experimental condition leaders will receive intensive training on the intervention including a five day workshop and guided training and practice under the supervision of experienced interventionists. Training will include in-depth review of the meaning of each item in the assessment instruments presented by ACASI, intensive review of the intervention ““Protect Your Family” manual, the PMTCT protocol, and use of cognitive behavioral intervention strategies in the intervention as well as how to manage sensitive issues (e.g., disclosure, IPV, gender dynamics, sexual risk reduction, safer conception practices). Training in the behavioral intervention strategies related to enhancing couple communication, medication adherence per the PMTCT protocol, sexual negotiation, couple disclosure of HIV status and reproductive health will be guided by the manuals created during the pilot study. Training includes practice for facilitation and support for HIV serostatus disclosure during counseling sessions. Following the workshop, each group leader will conduct two series of group sessions and couples counseling sessions under the supervision of the HSRC trainers (Sifunda, Mlambo, Matseke). “Protect Your Family” manuals will be adapted for individual women during project onset (see Formative Development).

Control condition leaders will receive an identical 1 day training session on use of ACASI technology. In addition, leaders will receive a 4 hour orientation to enable them to conduct time-equivalent group sessions comprised of childhood disease prevention videotapes (e.g., measles, diarrhea management, immunizations).

2.3 Condition Assignment: Intervention vs. Control

The 6 experimental condition CHCs will provide PMTCT plus the “Protect Your Family” intervention, the 6 control condition CHCs will provide the PMTCT standard of care plus a time-equivalent attention-control condition on disease prevention. Sites will be stratified by clinic volume and randomized.

2.3.1 Phase I: (women only enrollment)

Intervention (women only), the 6 experimental clinics will offer the standard of care (PMTCT), plus an intervention to HIV+ pregnant women (n = 360).

Control (women only), the 6 control clinics will provide the standard of care (PMTCT), plus health videos to HIV+ pregnant women (n = 360)

2.3.2 Phase II: (couples enrollment)

Intervention (couples) the 6 experimental clinics will offer the standard of care (PMTCT), plus an intervention to HIV+ pregnant women and their male partners (n = 360 couples)

Control (couples), the 6 control clinics will offer the standard of care (PMTCT), plus health videos to HIV+ pregnant women and their male partners (n = 360 couples).

3.0 SELECTION AND ENROLLMENT OF SUBJECTS

3.1 Eligibility

3.1.1 Inclusion Criteria

Participants. HIV positive pregnant women (n = 720) and HIV positive pregnant women and partners (n= 720 couples) will be enrolled over 30 months. Each CHC will recruit 60 women, followed by 60 couples, over 30 months.

There are no exclusions based on literacy as all materials will be administered using ACASI.

Eligibility. Participants recruited will be HIV seropositive pregnant women with partners, 20-24 weeks pregnant (typical time of entry into ANC care), aged ≥ 18 .

- In Phase 1 (women only), only women will be enrolled in the study.
- In Phase 2 (couples phase), both women and their partners will be enrolled. For the purposes of this study, primary male partners are defined as 1) husband, 2) current baby's father, or 3) current sexual partner. Women whose partner do not complete the baseline assessment will be disqualified from the study, given that Phase II eligibility criteria states that the woman is to be enrolled with a partner.

3.1.2 Exclusion criteria

Participants: Persons actively psychotic (auditory or visual hallucination) or intoxicated (e.g., under the influence of alcohol or illegal drugs) will not be eligible and will be referred for treatment. Following resolution of symptoms, these persons will be eligible for the study. N.B.: Any person presenting for sessions actively psychotic or intoxicated will be referred for treatment and will not be eligible to participate in sessions until symptoms are resolved due to reduced likelihood of benefit from sessions.

3.2 Recruitment

Per South African PMTCT Protocol, all women receive pre- and post-HIV counseling and testing (HCT) and, if HIV+, referral for CD4 assessment and ART;

- Study-eligible women candidates will be referred to the study assessor by PMTCT/HCT staff post-HIV testing and referral for treatment.
- Seropositive women with partners who have completed HCT will be approached to participate in the study; male partners in the couples phase will be invited to attend by their female partners following initial contact with the recruiter. Those agreeing to participate will be offered an appointment, and enrolled following provision of Informed Consent, maintaining confidentiality of the serostatus of both couple members. Per the standard of care, male partners will be encouraged, but not required, to undergo HCT.

3.3 Consenting and Enrollment Procedures

3.3.1 Interested participants contacting recruiters will be referred to study staff for pre-screening, and will be asked to provide screening information (see Eligibility) to determine if the person meets basic inclusion and exclusion criteria.

3.3.2 Screening tools for verification of eligibility will be used by the study recruiters. Study recruiters may utilize patient medical records and participant interview to establish eligibility.

Screening tools for verification of couples status. During Phase II, which includes male enrollment, all couples will be verified as being couples using the couples screening tool. Couples will be screened individually and both members will each be asked a series of three rotating questions which will identify them as a couple.

3.3.3 Persons who meet eligibility criteria will be given a detailed description of the study procedures, including time requirements and procedures to maintain confidentiality and will be scheduled for enrollment and assessment, at which time they will be further informed about the study and sign the Informed Consent form and complete a baseline assessment.

3.3.4 Orientation and Informed Consent and Baseline Assessment will be held at the project offices (on an individual basis); the staff member will describe the nature of the study to

prospective participants, assure them of the confidentiality of all data and test results, and inform them that they may refuse participation at any time.

All participants will be consented by having the study consent read to them to ensure comprehension by both literate and illiterate members. A signed or marked consent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be offered to the participant and provided at their request and this fact will be documented in the subject's record in addition to method of administration of consent. Participants who do not wish to retain a copy of the consent form will not be required to receive a copy.

The informed consent is reviewed in detail and actually read aloud to the prospective participant in their primary language. Each study candidate is asked to recount the essential content of the informed consent back to the staff member using a consent comprehension test, and agreeing to the terms of the consent before signing the form. Witnesses to consent will be drawn from study staff. Participants will have been briefed on the nature of the study prior to referral for informed consent.

The following questions will be used to evaluate comprehension of Informed Consent.

Purpose: Can you tell me in your own words what this project is all about?

Procedure: Can you tell me how many times you are expected to come to the study site?

Can you tell me how long you will be coming?

Risks: Can you tell me if there are any risks in participating in the study?

Compensation: Can you tell me if there is any compensation for coming?

Confidentiality: Can you tell me how your records will be kept safe?

Summary: Do you have any questions or concerns about the study?

3.3.5 Enrollment, post-consent: **Each qualified participant must sign an informed consent form prior to study enrollment and engagement in study related activities.*

- Complete a study information sheet. The participant's record of address, telephone number and contact person information is kept in a separate file.
- Assign participant number. Each participant will be assigned a unique and individual participant ID number. The participant will be given a card with the code number on it and will be instructed to bring this card to all visits.
- Complete or schedule a baseline assessment. Each participant is scheduled for a baseline psychosocial and behavioral assessment (completion of questionnaire battery), or will complete the assessment immediately following enrollment.
- Provide a medical release of information. All participants will be asked to provide a release to enable assessors to access data to verify incidence and dates of clinic visits, infant immunizations, and maternal and infant health status (VL where available, CD4, clinical stage, ART regimen, clinic attendance, intrapartum ART, infant NVP, CTX therapy,

adherence to maternal and infant ARVs, adherence to CTX therapy, infant weight, height, feeding).

Failure to enroll post screening: Participants who complete informed consent but do not complete enrollment will be entered into the database as a screening failure.

Participant Status Monitoring Report: A record of all participants screened and enrolled will be recorded in the participant monitoring database documenting each participant's current enrollment status.

4.0 HUMAN SUBJECTS

4.1 Institutional Review Board (IRB), Research Ethics Committee (REC) Review, Provincial Health office Review.

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB and RECs responsible for oversight of the study.

4.2 Participant Confidentiality

All screening forms, reports, audio tapes, data and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the DHHS, IRB, REC, NICHD or the SA sites.

Biological, psychosocial and behavioral data will be collected during the course of the study via clinic medical records, interviews and questionnaires. Study assessments will utilize the SOC assessment in which visits are aligned with study time points. Data will be coded with ID numbers only, and linkage data will be stored separately for tracking. No unique identifiers will be maintained with the samples or together with the data; access to collected data will be restricted to study staff only. The quantitative assessments will be overseen at the sites by trained study staff. All UM and HSRC study staff must complete human research participation training.

Confidentiality. Each participant will receive a card with a code number on it upon entering the study and will be instructed to bring this card to all visits. Participant ID numbers will be used to identify all participant files, with all other identifiers removed. Access to the computer data files will be by password codes. At each health assessment visit, the participant will reveal the code number and name so files can be updated. The list translating participant number to identifying information will be maintained in a secure locked file in the office of the Project Director, Mr. Ramlagan, at the HSRC. Additionally, in order to be able to track participants across the longitudinal period of the project, we will keep a separate record of each participant's address and contact person information and participant number. This record will indicate whether or not a participant has completed an assessment but will not include any assessment data. Participants will be made explicitly aware at the time of the informed consent of the nature of the two separate records that will be kept for them. Copies of the list of participants with ID numbers at each site will be retained by the site staff member for ACASI data entry; lists will be kept in a locked file cabinet at the clinic site and not leave the site at any time. To further assure confidentiality, this master list will not associate participant codes directly with subject names. Instead, a mathematical

transformation will be used to systematically modify the participant code number associated with a name so that casual observation will not enable linkage of name to data.

4.2 Participant Compensation

Participants will be compensated SA Rand 50 (~US\$5) per assessment for their time and transportation, and be provided snacks during sessions. All study visits (enrollment, assessments & sessions) will also be offered Saturday afternoons to enhance male participation.

4.3 Benefits and Risks

Potential risks to participants in this study are negative consequences they could suffer if confidentiality of information obtained in the study (including subject identity as a research participant) were breached. A number of steps will be taken to protect the confidentiality of participant data and identity. Research staff will attend training sessions by the study investigators and receive ongoing supervision in areas related to ethical conduct, confidentiality protection, and other topics of human participant protection. Interviewers will be therefore be trained to explain the purpose of the review to potential respondents, obtain informed consent, and inform respondents about their rights and benefits in a factual and neutral way without coercion to participate. Interviewers will inform potential participants about the confidentiality measures put in place to protect their privacy. All interviews will be anonymous and confidential and conducted in a private area inside the clinic area. No identifying information will be entered on the questionnaire. Interviewers will sign a confidentiality agreement stating they agree to keep the information obtained or viewed confidential. All research data obtained from participants will be labeled with a code number and not the participant's name. Only the number will appear on measures, data records, and computer files.

All data will be taken weekly to the offices of the HSRC by staff courier for data entry and storage.

Intimate Partner Violence (IPV).

Participants in the study may also be at risk of intimate partner violence (IPV), which occurs more frequently among pregnant women, women living with HIV and women in South Africa. Women who have recently discovered they are HIV+ may also be at increased risk of psychological stress and may choose to disclose their serostatus to partners, placing them at greater risk of IPV. The protocol established in our previous study on this topic was as follows -

Staff will be provided with training on prevention of IPV, planning for safety, removal to safe houses, reporting IPV to health care and police, and procurement of restraining orders (stay away). Additionally, for this study, staff will receive additional training through POWA (People Opposing Women Abuse, an NGO throughout South Africa) on techniques to ensure safe outcomes in situations in which IPV may arise following disclosure or other conflict.

The following protocol has been established in South Africa by the government with regard to testing and disclosure -

Pregnant women receiving mandatory HIV testing at the antenatal clinic are asked to test with their current partner, and disclosure is facilitated by the HIV Voluntary Counseling and Testing counselor. All HIV+ women are then referred for ARV medication for HIV to be received during pregnancy. South Africa law mandates that all persons receiving ARV medication disclose their HIV status to ONE

OTHER PERSON (e.g., partner, family member, friend) who acts as their support person while on ARV. This may increase the likelihood of IPV.

South Africa law mandates that a woman cannot be forced to disclose her status to her partner by health care providers (or this study).

Study protocol on request for HIV Couples Testing.

Women may be more likely to voluntarily disclose their serostatus while participating in the study. In the event that the study enrolls a woman who has not disclosed her status WHO WISHES TO DO SO, the study staff member will accompany the women to the HIV VCT Counselor (see above). The VCT Counselor is specially trained in facilitating disclosure and is mandated by SA Law to assist in the disclosure process with the current partner.

Following disclosure, or at any time during participation in the study:

In the event that the woman (or man) discloses that they are at risk of IPV: The study staff member will review with the participant the techniques on prevention of IPV, planning for safety, removal to safe houses, reporting IPV to health care and police, and procurement of restraining orders (stay away), and provided with the phone numbers for the POWA hotline and the police. Study staff members will be specially trained on these procedures.

Participants will incur no appreciable physical risks, other than those related to their existing use of prescribed ARV medications and the completion of psychosocial questionnaires or blood testing.

Physiological discomfort may be experienced through participation in this study during blood sampling and bruising may occur at the puncture site.

Strict confidentiality procedures will be set in place ensuring all communication and correspondence with participants so as to minimize participant stigmatization.

Psychological discomfort may occur when participants are given specific HIV/AIDS-related information and participate in discussion sessions that may lead to some mild, transient anxiety.

Should any participant disclose that he/she is experiencing suicidal ideation or anxiety/depression: The participant will be immediately evaluated by a physician, counselor or other qualified health care provider at their clinic. Following this evaluation, if so deemed by the provider, the participant will be referred for further assessment and/or hospitalization, or, if not in immediate danger of harming him or herself, will be referred for outpatient counseling/treatment. The research sites have access at all times to licensed psychiatric nurses and social workers, as well as psychiatrists and clinical psychologists at the district hospital. Some participants may manifest signs of HIV disease progression throughout the study, and may experience affective distress related to illness state. In our previous and ongoing studies, we have found that the frequency of occurrence and/or severity of any of the potential risks listed above have been minimal.

Potential benefits to participants include information and experiences that optimize treatment engagement, medication adherence and disease management. Potential benefits to participants include information and experiences that optimize sexual health status. Participants should benefit from training in anxiety reduction, coping skills, discussion of healthy sexual behaviors and social/interpersonal functioning as well as non-specific effects of membership in a supportive group

under the guidance of trained interventionists. The goal of this study, prevention of mother to child transmission of HIV, is also a potential benefit of study participation. Participants may benefit from training in adherence strategies, problem solving skills, discussion of HIV-related issues and social/interpersonal functioning as well as nonspecific effects of membership in a supportive group under the guidance of trained interventionists.

4.4 Study Discontinuation

The study may be discontinued at any time by the REC, IRB, the NIMH, or other government agencies as part of their duties to ensure that research subjects are protected.

5.0 STUDY INTERVENTION

“Protect Your Family” Intervention plus PMTCT Standard of Care (SOC). **No medications will be dispensed in this study.*

5.1 Intervention: Content and Duration

“Protect Your Family” intervention is a manualized, closed, structured behavioral risk reduction program targeting HIV, stigma, disclosure, communication, IPV, PMTCT knowledge, safer conception, family planning and dual method sexual barrier use.

Intervention participants will attend 3 prenatal weekly 2 hour gender-specific (male or female, 5-7 participants) *group sessions* followed by 1 individual *counseling session* and 2 monthly *couples or individual (women-only) counseling sessions* (1 prenatal, 2 postpartum) led by study-trained clinic staff (e.g., nurses, HCT counselors) plus SOC. The intervention strategies are in accordance with the SA PMTCT 2010 Guidelines (SA, 2009), PMTCT Expert Panel (2010) and Guidance for Healthcare Providers (Engender Health, 2008).

5.1.1 Group sessions. Sessions address prevention of vertical transmission, the importance of adherence to PMTCT and medication use, family planning, safer conception, infant feeding, HIV testing of family members and prevention of transmission of HIV. Participants receive cognitive behavioral skill training addressing the key components of each session, e.g., how cognitions relate to anticipated outcomes and thereby predict behavioral change. Group members are encouraged to problem solve, providing supportive feedback and peer mentorship on session topics. During Phase II, session topics for men’s and women’s groups are comparable, but place different emphasis on gender relevant topics, e.g., women focus on PMTCT protocol and medication adherence; men focus on HIV testing, alcohol and drug use. Participants will role play communication strategies and complete communication and negotiation homework using strategies practiced in the group sessions. Emphasis is placed on the sequence of communication, disclosure and avoiding IPV, e.g., women focus on prevention of IPV and conflict resolution, while men focus on anger management and prevention of IPV; both identify the antecedents of conflict and IPV as a method of prevention. Women establish a “safety plan” for responding to the threat of IPV, and are encouraged to address concerns about personal safety with clinic staff during study participation. Intervention information is presented with opportunity to practice new communication strategies and receive feedback (e.g., discussion of the pros and cons of disclosure, sharing experiences on partner’s responses).

[N.B.: Men's sessions do not address topics from the perspective of having a partner with HIV, and do not jeopardize their partner's HIV status.]

Group Session 1: HIV informational review, HCT (men's focus), PMTCT, infant feeding, ARV medication initiation/management (women's focus), communication strategies for sensitive topics, HIV status disclosure, avoiding IPV. Cognitive/behavioral (CB) skill training heightens participant awareness of their reactions to PMTCT and communication. Participants receive a week's supply of male & female condoms from clinic supplies.

Group Session 2: PMTCT discussion, HIV stigma, disclosure, family planning & ART (women's focus), HCT, alcohol and drugs, communication (men's focus), prevention of IPV. CB skills are applied to improving communication techniques. CB skills are used to address anxiety regarding HIV status disclosure and safer conception negotiation, including family planning post-partum. Participants receive a week's supply of male and female condoms from clinic.

Group Session 3: PMTCT, HAART, HCT discussion, family planning, safer conception, dual barrier methods & disclosure (women's focus), conflict resolution & anger management (men's focus), communication & reducing/avoiding IPV, cognitive behavioral skill training, and importance of health facility delivery and PMTCT medications at birth. CB exercises and role plays use participant experiences in problem solving, and participants are guided in applying cognitive restructuring skills to conflict resolution, communication, safer conception, and HIV disclosure. Participants receive a week's supply of male and female condoms from clinic.

- 5.1.2 Counseling sessions.** Three, structured one-hour sessions are led by study-trained CHC staff with couples or individuals (women-only). The first session is an individual antenatal session and two additional sessions (during Phase II, including male partners) occur 6 weeks and 3 months post-natally. Information concerns adherence to the PMTCT protocol, e.g., infant feeding practices and medication, and reproductive decision making, e.g., fertility planning, safer conception practices. Each session enhances Motivation to adhere to the PMTCT protocol, i.e., the necessity to adhere to the protocol throughout the infant's first 6 months of life, or longer, as determined by the child's health and feeding status. Each session also addresses reducing risk Behavior related to unintended pregnancy, acquisition of STDs and prevention of STD/HIV transmission to partners, and use of dual methods of protection (i.e., consistent use of condoms along with another safe contraceptive method) regardless of partner serostatus.

[N.B.: Counseling sessions focus on family planning and dual protection methods, infant feeding practices and safer conception that will not compromise participants' confidentiality.]

CounselingSession 1: Week 32 Antenatal . Review of PMTCT protocol (adherence to medication, infant feeding practices). Importance of health facility delivery & NVP at delivery. Reproductive decision making: discussion of fertility intentions & safer conception practices.

Counseling Session 2: 6 weeks Post-natal. Review of PMTCT protocol (medication, infant feeding). Discussion of safer conception practices and family planning using dual barrier methods.

Counseling Session 3: 3 months Post-natal. Review of PMTCT protocol (medication, infant feeding) and review of use of safer conception and risk reduction practices.

5.2 Control & PMTCT Standard of Care.

Participants will receive PMTCT SOC plus a time-equivalent, group-administered video presentation on health promotion and disease prevention (e.g., measles, diarrheal management, dysentery/dehydration, immunizations/vaccinations) in 3 group sessions, followed by 3 couple or individual women sessions on disease prevention.

6.0 CLINICAL AND LABORATORY EVALUATIONS

All assessments target PMTCT objectives and will be presented using ACASI technology to enhance disclosure of sensitive information and account for literacy issues. All study materials, e.g., consent, assessment and intervention, will be translated into local languages (Zulu & Sotho) or were translated during the pilot study. Participant assessments include both psychosocial assessments and biological and clinic data at study entry, pre-delivery (32 weeks pregnant), 6 weeks, and 6 & 12 months post-natal follow up.

6.1 Schedule of Assessments

Domain	Instruments	TIME (min)	Base-line	32 weeks pregnant	6 weeks Post-Natal	6 mo Post-Natal	12 mo Post-Natal
HIV status	HCT: Mother (entry eligibility) HCT: Father (optional) PCR: Infant		X X		X		X
Retention in Care	Clinic record abstraction Clinic attendance Questionnaire Road to Health Booklet	0 5 0		X	X	X X X	X X X
Intervention Attendance	Attendance Questionnaire Attendance Checklist Review	5 0		X X			
ART Adherence: Mother + Infant	Dried Blood Spot: Mother Dried Blood Spot: Infant Adherence rating & Visual Analogue Scale ACTG Adherence Instrument	5 5 5 5		X X X X	X X X X	X X X X	X X X X
Demographics	Demographic Interview	5	X				
Infant Health Status	Infant health Questionnaire	5			X	X	X
Male HIV Status	Male HIV Questionnaire	5	X	X		X	X
Postpartum Depression	Edinburgh Postnatal Depression Scale	5	X		X	X	X
Stigma	HIV/AIDS Stigma Instrument Externalized Stigma Scale	5	X X				X X
HIV Disclosure	Disclosure Scale	5	X	X		X	X
IPV & Communication	Conflict Tactics Scale	5	X	X		X	X
HIV & PMTCT Knowledge	HIV & PMTCT Knowledge Questionnaire	5	X	X		X	X
Contraception & Safer contraception practices	Sexual Barrier Use Diary Family Planning Assessment	5 5	X X	X X		X X	X X
Infant Feeding	Infant Feeding Diary	5			X	X	X
Male engagement	Male Involvement Index	5	X	X		X	X

6.2 Biological Assessment & Clinic data.

- 6.2.1 HIV Status, clinic attendance & retention data:** Clinic data include 1) infant PCR HIV test at 6 weeks (clinic data) and HIV antibody test at 12 months (study administered HIV test); 2) paternal serostatus at baseline (optional testing, clinic data), 3) maternal ART regimen, and 4) PMTCT clinic visits (maternal, infant) and study session attendance (participant report and facilitator attendance checklist). PMTCT retention will be dichotomized based on WHO guidelines (2006): Attendance will be dichotomized at ≥ 4 prenatal and ≥ 4 postpartum clinic visits and compared to < 4 prenatal and < 4 postpartum.
- 6.2.2 ARV uptake assessment.** Maternal adherence will be assessed by blood sampling (dried blood spot, DBS) pre-delivery (32 weeks pregnant); infant adherence will be assessed at 6 weeks by DBS. DBS will assess presence of ARVs for those on ART lifelong medications (Tenofovir, Lamivudine, Emtracitabine, Stavudine, Lopinavir, Ritonavir, Efavirenz) and those on short term PMTCT ARVs (Nevirapine, Zidovudine). Samples will be analyzed to obtain a quantitative assessment of the presence of ARVs.
- 6.2.3 Road to health booklet.** All female participants will be asked to provide their “Road to Health” booklet at each assessment. Postpartum clinic visits, maternal ART prescription, intrapartum ARV provision, infant HIV status, infant ART provision, infant feeding, and infant immunizations will be confirmed from the booklet. In the event that the participant does not provide the booklet, this data will be collected from clinic records.
- 6.2.4 Study appointment log.** All participants will be provided a card to help participants keep track of study and clinic appointments. Facilitators and clinic staff will be asked to initial next to appointments as they are completed. Attendance at study and clinic appointments will be confirmed by reviewing this card.
- 6.2.5 Blood Sampling Procedures.** Study staff conducting assessments will complete a form providing information on the participant (study number, date, name of test, interviewer) for the patient providing a blood sample; a copy of this request will be placed in the participant’s file in the respective study office. Original lab-test request forms will be retained by the staff member and submitted to the lab along with the blood samples for testing.

6.3 Psychosocial Assessments.

Self-reported adherence – Mother & Infant is assessed using a self-report or maternal reported rating of adherence over one month, combined with a Visual Analogue Scale (VAS), used to assess adherence over the previous 7 days. Additionally, a modified version of the ACTG 4-day adherence instrument (Chesney et al., 2000) will be used to assess missed doses over the previous 4 days and reasons for missed doses in the past 3 months. Adherence will be analyzed as continuous as well as dichotomous (100% vs. $<100\%$) variables.

Demographics questionnaire is used to assess age, ethnic group, education, income, religion, marital/current partner serostatus, medication/ART status, children, children’s serostatus, living situation, pregnancy stage and due date, and alcohol use.

Infant Health Status is used to assess the baby's health at delivery and following. The location and time of delivery is also assessed, as well as whether or not the baby was tested for HIV.

Male HIV Questionnaire assesses male HIV testing and HIV serostatus

Stigma is assessed using an adaptation of the WILLOW HIV/AIDS Stigma Instrument and measures perceived and enacted stigma in the home, community, workplace and health care settings. Stigma is conceptualized as internal (e.g., self-exclusion from services and opportunities, social withdrawal, and fear of disclosure) and external (e.g., avoidance, rejection, and abuse). The AIDS-Related Stigma Scale (Kalichman et al., 2009) is also used to measure stigma.

Postpartum Depression is assessed using the 10-item Edinburgh Postnatal Depression Scale (Cox, Holden, and Sagovsky et al., 1987). Pregnant women and mothers indicate the frequency of depressive symptoms over the past 7 days, and a score of 10 or higher indicates that the woman may be at risk for postpartum depression.

HIV Disclosure is assessed using an adaptation the **Disclosure Scale** (Visser et al., 2008) assessing disclosure among sexual partners and family members during pregnancy, and factors associated with disclosure, knowledge of partners' HIV status, and previous HIV counseling or education.

IPV & Communication are assessed using an adaptation of **Conflict Tactics Scale** (Strauss et al., 1979), an 18-item scale which assesses conflict resolution style over the current month and previous 12 months, in three domains of positive and negative interactions and violence.

HIV & PMTCT Knowledge is assessed using an adaptation of the **AIDS-Related Knowledge Test** (Fisher et al., 1996). This adaptation assesses HIV risk and prevention-related knowledge. Items reflect information about HIV transmission, reinfection with resistant virus, condom use, AIDS-related and PMTCT-specific knowledge and are responded to as True, False, Yes, No, or Don't Know. The AIDS knowledge test is scored for the number of correct responses, with "Don't Know" scored as incorrect.

Sexual Barrier Use is assessed using the **Sexual Barrier Diary**, which asks participants to recount their sexual activities, indicating for each day of the past week whether or not they had intercourse, and if so, the type of sexual barrier method used, if any. Sexual barrier use will be analyzed both as continuous and dichotomous (100% vs. <100%) variables.

Family Planning is assessed using an adapted survey on knowledge, attitudes and use of safer conception practices, including individual, interpersonal, sociocultural, structural factors (Idonije 2011). **Knowledge** items assess perception of risk of transmission to the partner during pregnancy as well as knowledge of the fertility cycle and ideal time to conceive. **Attitudes** items are adapted from Dommering et al. (2011) for women living with HIV, and assesses current and previous fertility intentions (FI), and factors associated with FI (e.g., perceived risk of transmission, perceived burden). A conjoint analysis survey is also used to assess family planning attitudes. **Practices** items assess whether the pregnancy was planned or unplanned, whether a provider was consulted prior to pregnancy, current use of family planning and intentions to engage in family planning in the future.

Infant Feeding is assessed using an adaptation of the WHO (2001) feeding scale measuring breastfeeding and replacement feeding practices used in the context of PMTCT in the last 7 days.

Male Engagement is assessed using an adapted form of the Male Involvement Index (Byamugisha et al., 2010; Peltzer et al., 2011), a 11-item scale assessing male ante-natal involvement, as well as group and couples counseling attendance.

6.4 Assessment Procedures: Timing Evaluations

6.4.1 Pre-screening referrals

- Prior to referral to the study, all female participants will have received pre- and post-test counseling for HIV (including facts on HIV, transmission, associated risks and implications of positive and negative results) and will have been referred for ART. Participants diagnosed as HIV seropositive will have received emotional support and referrals for services from clinic staff/counselors.
- Participants may be screened in-person and/or over-the-phone to determine eligibility prior to enrollment; screenings can also be conducted by the VCT clinic or the ANC clinic.

6.4.2 Enrollment Screening

- All participants will be screened to meet inclusion criteria.
- *Screening failures (participants who are screened and not enrolled) are documented in the participant status monitoring report.*

6.4.3 Entry Evaluations

- Upon enrollment, or following enrollment at a separate appointment, participants will complete a baseline assessment battery (including psychosocial and behavioral assessments) under the oversight of trained assessors. Participant medical records will be assessed as outlined above.
- **For Phase II (couples phase): After the woman completes the baseline assessment, the male partner should complete the baseline assessment within 2 weeks of the woman's assessment. Both the woman and male partner's baseline assessments should be completed before the woman or her male partner participate in any aspect of the intervention.**

6.4.4 Post-Entry Evaluations

- Participants will complete assessments (including psychosocial and behavioral assessments) under the oversight of trained assessors at baseline, 32 weeks pregnant, 6 weeks post-partum, 6 months post-partum and 12 months post-partum. All assessment completions will be documented in the patient record. All infants will provide blood samples at 6 weeks and 12 months; mothers will provide a blood sample at 32 weeks gestation.

6.4.5 Study Completion Evaluations

- Participants will complete an assessment battery (including psychosocial and behavioral assessments) and infants will provide a biological assessment (blood sample) at 12 months post baseline.

6.4.6 Discontinuation Evaluations

- There are no evaluations required for participants who discontinue to the study. Participants who voluntarily withdraw are documented in the participant status monitoring report, noting the

reason provided by the participant for withdrawal from the study (example, relocation, busy work schedule, feeling uncomfortable) in the study monitoring report.

- Study participants who are randomized and fail to complete their initial session will be noted as screening failures and all necessary documentation will be completed in the patient study monitoring report.

6.5.3 Participant Contact: Procedures for follow-up

- **Scheduling.** Participants are contacted prior to the session to remind them of the upcoming session.
- **Missed Intervention/Control Group Sessions.** Missed sessions cannot be rescheduled for a later date.
 - Following a missed intervention/control session, participants are contacted the following week to remind them of the next session. During scheduling, participants should be told they were missed at the last session.
 - Participants should not be asked why they missed a session by phone or at the next session date.
- **Missed assessments.** Participants who miss an assessment, cannot be reached for scheduling, or fail to appear to complete an assessment post-intervention, or at follow-up assessments, are followed-up and contacted by phone to reschedule the assessment for another more convenient date for the participant.
 - Participants may complete a missed mid-point assessment up-to one month after the scheduled assessment date.
 - Participants may complete a missed end-point assessment up to two months after the final scheduled assessment date.
 - Participants should not be asked why they missed an assessment by phone or at the next session date.
- **Phone Contact for new or missed appointments.** Participants may be contacted by 2 phone calls, and 1 call to alternative persons or phone number provided at enrollment, if the participants phone is no longer active. All attempts are documented in a phone contact log.

7.0 DATA MANAGEMENT AND ADVERSE EVENT REPORTING

Participants will not be identified by name on any study related documents or files (with the exception of the 1 copy of the linkage file with participant name and ID numbers kept in the project director's office under lock and key).

7.1 Records to be Kept

7.1.1 Participant Status Monitoring Report (PSMR)

The PSMR will be used to maintain tracking of each research participant status of enrollment in the study. Information on the PSMR includes: date of study start, visit attendance, withdrawal, loss to follow up, reason for loss to follow up.

7.1.2 Participant Files

Each participant will have an individual file at the study site in a secure office. All participant information sheets, and any other study related record will be kept in the participants file.

7.1.3 Participant Contact Log

Each participant will have a contact log where all contact attempts will be recorded.

7.2 Role of Data Management

7.2.1 Oversight on recording, entering and transmitting study data

All newly captured data will be provided weekly to the offices of the HSRC by staff courier for upload and storage. Updated data files will be provided to the Miami site weekly by the Project Director at HSRC, Shandir Ramlagan. All data will be submitted using an established password-protected Dropbox account.

All clinic medical record data will be entered into the data set within one month of the associated study visit. It is the responsibility of the Data Managers at UM, Ryan Cook and Andrew Spence, to oversee and assure the quality of data collected. This role extends from protocol development to generation of the final study databases.

During data entry, all laptop computers will be secured with a lock; the site staff will be responsible for the security of the laptops. Laptop computers will be retained in a locked cabinet at the study site and all data with participant identifiers (name, address) will be locked in a separate cabinet to safeguard participant confidentiality with regard to access to the study records. Data entered onto computers will have no identifiers, but all computers with data will be password protected.

7.3 Clinical Site Monitoring and Record Availability

7.3.1 Program officers under the National Institute of Child Health and Human Development (NICHD) may visit the participating clinical research sites to review the individual subject records, including consent forms, CRFs, supporting data, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records.

7.3.2 The site investigator will make study documents (e.g., consent forms, CRFs) and pertinent records readily available for inspection by the local REC, IRB, monitors, the NIHCD, the Office for Human Research Protections (OHRP) for confirmation of the study data.

7.4 Adverse Event Reporting to IRBs

Adverse events will be reported to the study PI and forwarded to the IRB/REC within 48 hours of the report being received by the study staff at the project site. AEs will be reported on the Adverse Event Reporting form by the UM PI.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Study Discontinuation.

The study may be discontinued at any time by the DSMB, IRB, the NIH, or other government agencies as part of their duties to ensure that research subjects are protected.

8.2 Permanent Treatment Discontinuation

- Reaching a defined clinical endpoint (*as applicable*). YES
- Completion of treatment as defined in the protocol. YES
- Request by subject to terminate treatment. YES
- Clinical reasons believed life threatening by clinic health care workers or study staff. YES

8.3 Premature Study Discontinuation

- Failure by the subject to attend [*any*] consecutive clinic visits. NO
- Subject repeated noncompliance with study procedures as prescribed. NO
- Pregnancy or breast-feeding (*if applicable*). NO
- Request by the subject to withdraw. YES
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject. YES
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results. NO
- A defined study endpoint reached (*if applicable*) YES
- At the discretion of the IRB, REC, NICHD, investigator. YES

9.0 Program Evaluation & Dissemination

9.1 Quality Assurance/Quality Control

Quality control will be overseen by project staff, and intervention fidelity will be maintained by audio recording of intervention sessions, interventionist checklists and weekly review by Ms. Mlambo. Evaluation will include review of a random sampling of 10% of the intervention audio recordings and weekly feedback to group leaders. Research staff with bilingual target language skills will transcribe the recorded sessions using headphones in private rooms at the HSRC offices. Dr. Jones will also conduct

QC of a 10% sample of transcribed sessions and provide monthly feedback to Ms. Mlambo. Ongoing contact with CHC staff will allow SA team members to respond to questions on study protocol and to discuss and resolve any difficulties that may arise. Monthly conference calls between US and South Africa will address clinic issues including fidelity to protocol and resolution of problems (see Leadership Plan). Semi-annual visits by Miami study investigators will include review of protocol implementation with Drs. Peltzer, Dwane, study personnel and CHC staff.

9.2 Challenges & Solutions

Ongoing project staff/CHC meetings will be used to assess and respond to challenges as they arise. Challenges and solutions for implementation are described, and include 1) attainment of recruitment goals: if needed, additional sites have been identified for recruitment in neighboring Ehlanzeni District, 2) retention in care: our previous pilot study achieved 95% retention over 12 months utilizing a protocol of active participant contact and updates to participant locator information at each visit which will be utilized in the proposed study, 3) non-HIV disclosure prior to couples counseling session: a protocol will be established prior to counseling on maintaining HIV confidentiality, 4) IPV risk: the pilot study established a protocol to respond to IPV and threats of violence that will be utilized in the current study; [N.B.: Pilot study found a reduction in IPV and negative communication in the experimental condition], 5) contextual and health system challenges: study investigators and staff will engage local stakeholders, community advisory boards, leadership of CHCs and Provincial MOH in the planning and implementation process, 6) clinic site staff turnover and space limitations: clinics and CHC staff will be supported in the designation of devoted space for groups, and the identification of qualified staff to participate and the use of the train the trainer model to provide additional trained staff to anticipate potential staff turnover.

9.3 DSMB

A Data Safety Monitoring Board (DSMB) will be established prior to study onset. The Board will include two members, one from the HSRC in SA and one from the University of Miami in the US, neither of whom will be directly connected with the study. Administrative reviews will be conducted at the midpoint of each phase; board members will review the data to determine: 1) if there are any unexpected systematic variations in health status attributable to either study condition which may be negatively affecting the health of the participants; and 2) whether the experimental condition (or control) are demonstrating such clear-cut positive effects that continuation of the trial (i.e., withholding the effective treatment from half of the participants) would be considered unethical. Prior to the initiation of the study, the Project Executive Committee will appoint members for the DSMB; the DSMB and Project Executive Committee will develop stopping rules to ensure participant safety.

9.4 Implementation, Sustainability & Generalizability

If successful in reducing MTCT, the study investigators will meet with the sub-District, District, and Provincial health officials to promote the translation of study findings into health policy recommendations. The investigators will promote program implementation and scale-up at other health centers within Mpumalanga and other South African provinces (e.g., KwaZulu-Natal) with notably elevated rates of MTCT. The intervention manual, train the trainer model for clinic staff and QC materials provide a framework for implementation and sustainability for CHC staff as both implementers and trainers. This strategy will enable rapid scale-up into other ANC/CHC/hospital venues at District, Provincial and National levels.

Current studies support the sustainability of skill building programs for CHC staff to achieve expanded scope of practice (e.g., Uwimana et al., 2012a; Peltzer et al., 2009; 2010). The DOH now

employs at least 5 paid, trained, certified community health workers per clinic rather than relying on volunteers, who will be available to implement the intervention on a large scale (e.g., Nxumalo et al., 2013; Ndou et al., 2013; Uwimana et al., 2012b).

10.0 STATISTICAL CONSIDERATIONS

10.1 Primary Endpoints (including definitions)

Independent variables

Condition assignment (experimental, control)

Partner participation (male involvement)

Time (Baseline, 32 weeks gestation, 6 weeks postnatal, 6 months postnatal, 12 months postnatal)

Dependent variables

HIV serostatus

Clinic attendance

Sexual risk behavior

ARV medication adherence

Retention in care

Infant feeding practices

Safer conception practices (family planning)

Moderating variables

Male partner serostatus

Time on ART

HIV disclosure

IPV

Communication style

Postpartum depression

10.2 Specific Aims and Hypotheses

Specific Aim 1: to increase uptake and adherence to ante-, peri- and post-natal PMTCT protocols by HIV positive pregnant women through the implementation of a comprehensive, evidence-based risk reduction, medication adherence and PMTCT intervention.

Hypothesis 1.1: Within each Phase, Experimental condition mothers will be significantly more likely to adhere to PMTCT protocol medications as prescribed compared to Control condition mothers at 32 weeks pregnant and 6 and 12 months postpartum, and provide them to infants up to 6 weeks.

Hypothesis 1.2: Within each Phase, infants born to Experimental condition mothers will be less likely to test HIV+ at 6 weeks and 12 months of age compared to those born to Control condition mothers.

Specific Aim 2: to retain women and infants in post-natal care to ensure adherence to PMTCT safe infant feeding protocols (SA DOH, 2010).

Hypothesis 2: Within each Phase, experimental condition mothers will be more likely to continue PMTCT safe infant feeding at 6 months and more likely to be retained in care at 6 and 12 months postpartum compared to control condition mothers.

Specific Aim 3: to improve sexual and reproductive decision making and safer conception practices.

Hypothesis 3: Within each Phase, Experimental condition mothers will decrease unsafe sexual practices and/or increase and maintain the use of safer conception practices (e.g., dual barrier methods) at 32 weeks pregnant and 6 and 12 months post-partum compared to Control condition mothers. This will be accomplished with no increase in intimate partner violence.

Specific Aim 4: to assess the impact of male engagement on PMTCT uptake (medication adherence, feeding practices, clinic attendance), safer sex and family planning practices.

Hypothesis 4: Within the Experimental condition, mothers in Phase 2 (couples arm) will a) be more likely to take PMTCT medications at 32 weeks pregnant and 6 and 12 months postpartum, and provide medications to their infants up to 6 weeks; b) be more likely to continue safe infant feeding and be retained in care at 6 and 12 months; and c) be more likely to increase safer sex and/or safer conception practices at 32 weeks pregnant, and 6 and 12 months in comparison with mothers in the Experimental condition Phase 1 (women-only arm).

10.3 Analytic Plan: The study tests an intervention to reduce vertical transmission by enhanced PMTCT uptake using an intent to treat model. A cluster randomized design will be used, with 12 clinics stratified by size and randomly assigned as 6 intervention and 6 control clinics with 60 women (Phase 1) and 60 couples (Phase 2) per clinic. Preliminary analyses will include descriptive statistics, e.g., means, standard deviations, frequencies and percentages as well as t-tests, chi-square tests, Pearson's correlations of factors associated with sexual risk behavior, medication adherence, retention in care and vertical transmission. Factors considered as potential confounders are those observed to have moderate associations with outcome variables in preliminary tests of association, using a conservative α of 0.20 for significance testing. These variables will be controlled in analyses as appropriate and assessed independently, e.g., male partner, male partner serostatus, HIV disclosure, IPV, communication style. Prior to analyses, appropriate variable transformations will be applied to outcome variables in order to satisfy distributional assumptions. SAS (SAS Institute, Inc., Cary, NC) and SPSS (Statistical Packages for Social Sciences, IBM) will be used for all analyses using the 0.05 level to determine statistical significance. These analyses have random terms that account for variation caused by treating subjects in a group and in a clinic (individuals nested within cohorts; cohorts are clustered in clinics); these are random terms in the analytic models. The following hypotheses will be adjusted for the clustering effect.

Analytic Approach: In order to test the impact of the experimental condition within each Phase on the outcomes of Hypotheses 1.1, 1.2, 2 & 3, separate analyses will be conducted for the women-only Phase and the couples Phase. A series of generalized linear mixed models will be conducted to perform regressions with adherence, infant HIV serostatus, safe infant feeding, retention in care, safer sex, family planning practices as the outcomes and clinic, condition status (intervention vs. control), time, and the interaction of time and condition status as the fixed predictor of interest. The random effects will be persons nested within cohorts and cohorts nested within clinics. A heterogeneous autocorrelated covariance matrix will be used to represent the correlated data structure. A secondary analysis will test for moderating effects such as male partner, HIV serostatus disclosure, self-efficacy for disclosure, and male partner serostatus. Significant moderators will be kept in the final model. Planned comparisons will be made between groups at each time and between times within each condition or Phase. For Hypothesis 4, Phase 1 and Phase 2 will be compared using the same type of analysis on the intervention condition only, and include as fixed predictors Phase, time, and Phase x time interaction, utilizing the same random effect and covariance structure.

In order to test the relative contribution of ART adherence, safe infant feeding and retention in care on Infant HIV test outcome at 12 months, additional analyses for Hypothesis 1.2 will be conducted with a generalized linear mixed model, performing a logistic regression in which infant HIV test at 12 months

will be the outcome, and ART adherence, safe infant feeding and retention in care will be the fixed predictors of interest at 12 months with a random effect of person within cluster.

Based on our experience with this population (see Preliminary Studies), we expect to have complete data for baseline and post intervention. Retention rates for follow-up at 6 and 12 months are expected to be 95% at each time point. Therefore, we assume any missing data is random and non-informative. This type of missing data is permissible for mixed model analyses. Missing data will be reviewed for systematic trends within condition and controlled for, as appropriate.

10.4 Sample Size & Attrition, Power Analysis.

Sample size and attrition. The sample size of 720 pregnant women per phase was based on our experience in our previous PMTCT study, from which we anticipate a 16% miscarriage and infant death rate and a 5% attrition rate over 12 months (n = 156 lost; n = 564 retained).

Power Analysis. The power calculations for Hypothesis 1.1 used a pooled analysis of adherence studies that indicated a pooled estimate of 73.5% (95% confidence interval [CI] 69.3-77.5%, $I^2=97.7\%$) of pregnant women had adequate ($\geq 80\%$) ART adherence. The pooled proportion of women with adequate adherence levels was higher during the ante-natal (75.7%, 95% CI 71.5-79.7%) than during the post-partum period (53.0% to 95%; 32.8% to 72.7%) ($p=0.005$). Calculations for Hypothesis 2 are based on our pilot study data and local assessments (Ukpe et al., 2009; Ladzani et al., 2011), which identified 30-50% of sero-positive mothers providing mixed feeding post-natally. Our estimated sample size is based on infant serostatus at 6 weeks and 12 months. Averaged clinic data indicate ~13% of infants will be seropositive at 6 weeks and an additional 13% will be seropositive at 12 months of age. Using an HIV PCR rate of 13% at 6 weeks in the control arm, a power analysis for Hypotheses 1.3 and 3 indicated that 6 sites per group (6 experimental, 6 control) with an unadjusted sample size of 564 infants per phase would provide 80% power to detect a significant difference between conditions assuming reduction to 4% in the intervention condition and intracluster correlation coefficients (ICC) up to 0.02 (depending on the two rates) with a two tailed test at the 0.05 level (Klar & Donner, 2001). This calculation assumes Infant HIV PCR rates of 13% in the control arm and rates of 4% in the experimental arm at 6 weeks.

11.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by policies developed by the Project Steering Committee. Any presentation, abstract, or manuscript will be made available for review prior to submission.

12.0 PHARMACOLOGY PLAN

n/a

13.0 BIOHAZARD CONTAINMENT

n/a

14.0 REFERENCES

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